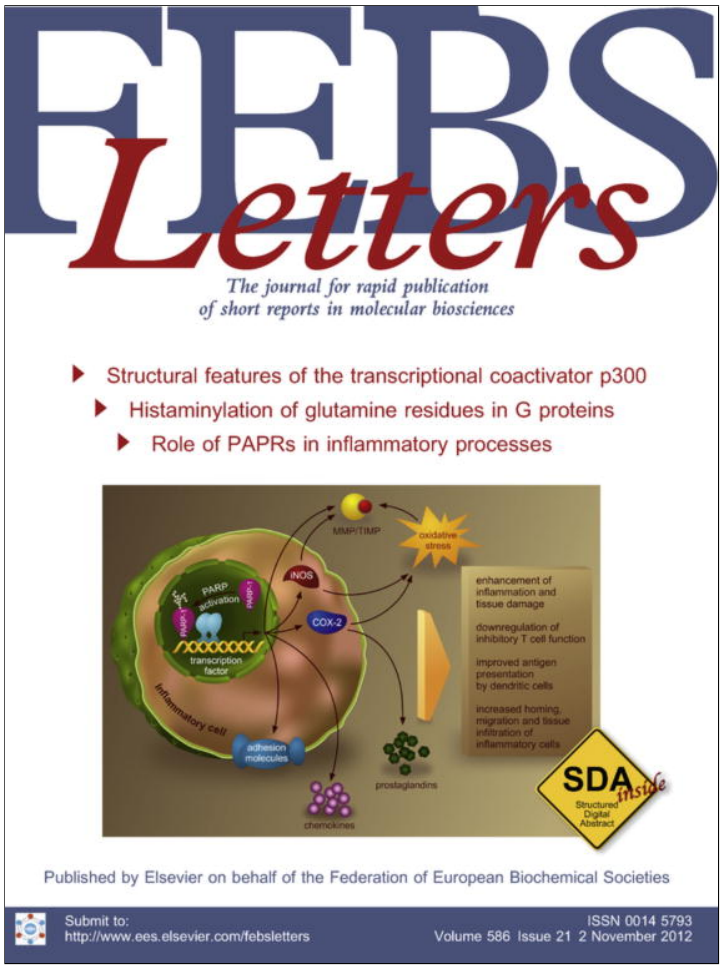

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Review

Role of poly(ADP-ribose) polymerases in the regulation of inflammatory processes

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ABSTRACT

PARP enzymes influence the immune system at several key points and thus modulate inflammatory diseases. PARP enzymes affect immune cell maturation and differentiation and regulate the expression of inflammatory mediators such as cytokines, chemokines, inducible nitric oxide synthase and adhesion molecules. Moreover, PARP enzymes are key regulators of cell death during inflammation-related oxidative and nitrosative stress. Here we provide an overview of the different inflammatory diseases regulated by PARP enzymes.

1. Introduction

Poly(ADP-ribose) polymerases (PARPs) constitute a family of 17 enzymes [1] sharing a highly conserved PARP signature motif in the catalytic domain. The prototypical PARP enzymes (PARP-1 and -2) possess a DNA binding domain enabling them to bind to damaged DNA and thus become activated [2]. Active PARP-1 and PARP-2 synthesize poly(ADP-ribose) polymers from NAD^+ marking proteins near the DNA damage site. Although the characterization of the newly discovered PARP enzymes has not yet been accomplished, it is already apparent that PARP enzymes perform a wide variety of tasks ranging from DNA repair, regulation of gene expression to cell death [3].

The anti-inflammatory properties of PARP inhibitors have been recognized over a decade [4] and the number of publications on these effects is still on the rise. Our aim in the present chapter is to provide an overview of the complex role of PARP enzymes in inflammatory processes ranging from immune cell maturation to inflammatory gene expression and to explain the mechanism of protection provided by the PARP knockout phenotypes or by PARP inhibition in inflammatory tissue injury.

2. Poly(ADP-ribose) polymerases in the maturation and differentiation of immune cells

In adult mammals immune cells are formed in the bone marrow by the division of resident stem cells. These premature immune cells then travel to different immune organs (thymus, the Peyer's patches of the gastrointestinal (GI) tract, etc.) and undergo a process called maturation in order to yield competent, functional, non-self reactive cells that can then exit to the periphery and perform adequate immune functions. Although no systematic investigation took place as of yet, current data suggest that different PARP enzymes are necessary for the maturation and differentiation of different immune cell types.

An important point during T and B cell development is the VDJ recombination that is responsible for the generation of a wide repertoire of immunoglobulins and T cell receptors. VDJ recombination involves DNA rearrangement and thus the resolution and rejoining of DNA strand breaks in which the elementary role of the DNA repair machinery has been shown [5] prompting research to assess the role of PARPs in these processes. Only minor alterations have been reported in B cells of PARP-1 knockout mice. However, PARP inhibition increased the frequency of Ig class switch [6] leading to variations in immunoglobulin class composition [7]. Moreover, the deficient VDJ recombination in the T cells of SCID (severe combined immunodeficiency) mice could be rescued by knocking out PARP-1 [8] indicating the antirecombinogenic effect of PARP-1 during T cell maturation.

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PARP-1 influences mature B cell differentiation and proliferation by binding to the *Bcl6* gene in a sequence-specific manner acting as a transcriptional repressor. Since Bcl6 expression is restricted to germinal centers, where active cell division takes place, PARP-1 binding and activation is likely to be necessary for B cells to exit from germinal centers [9].

Both T cell function and development may be affected by PARP-1 and -2. A recent report has described an increased number but normal phenotype and function of $Foxp3^+$ regulatory T cells and consequently impaired proliferation of $CD4^+$ T cells and suppressed IL-2 production in PARP-$1^{-/-}$ mice [10]. This may partly explain suppressed inflammation observed in PARP-1 knockout mice in models of T cell-mediated inflammatory diseases. T cell-dependent antibody responses were also found to be impaired in PARP-$1^{-/-}$ mice [7]. PARP-2 also affects T cell number through impairing thymopoesis. PARP-2 was abundantly expressed in the subcapsular zone of the thymus with decreased expression towards the center of the thymus suggestive of its involvement in thymocyte proliferation [11]. Indeed, PARP-2 deficient thymocytes die via p53-mediated apoptosis that leads to decreased number of $CD4^+$, $CD8^+$ thymocytes in the thymus [12,13].

Impaired T cell-mediated inflammation can thus be attributed to several factors, such as impaired inflammatory gene expression (discussed in the next chapter) and difference in the composition of T cell populations. Scattered data in the literature indicate that the differentiation of other inflammatory cell types, such as monocytes and dendritic cells may also be affected by PARP-1 [14,15].

3. Molecular events in inflammation regualated by poly(ADP-ribose) polymerases

3.1. Transcription factors

PARP enzymes interact with a large number of transcription factors of which many are involved in the regulation of inflammatory gene expression. The first one identified was NFκB [16] providing an explanation at the molecular level for the protection of PARP-1 knockout mice from endotoxin shock. Several other transcription factors and cofactors involved in inflammatory regulation such as NFAT [17,18], AP-1 [19–22], YY1 [23], sp1 [24], SIRT1 [25,26] were also found to be modulated by PARP-1. Recent data pointed towards the involvement of other PARP enzymes in the transcriptional regulation of inflammatory processes. PARP-2 regulates the activity of several members of the peroxisome proliferator activated receptor family (PPARs) [27], or SIRT1 [28,29], while PARP-14 mediates STAT6 transcription [30,31]. However, the relevance of these latter findings in inflammations requires further investigation.

It is interesting to note that most transcription factors listed above are also activated by oxidative stress, thus considered redox-sensitive. It is debated whether PARP activity is necessary for the proper activation of these transcription factors since in vitro data suggest that DNA binding and PARP activity might be dispensable for NFκB activation [32]. In contrast, a large set of in vivo data support the anti-inflammatory effects of PARP inhibitors. Recently two excellent studies linked PARP1 to upstream events of NFκB pathway by demonstrating that PARP-1 activation is necessary for the ubiquitination and degradation of the inhibitor of NFκB kinase (IKK) promoting NFκB activation [33,34]. The actual mode of how PARP-1 contributes to the activation of NFκB and other transcription factors in different models will require further investigation.

3.2. Cytokines and chemokines

Inflammatory cytokines such as TNFα, IL-1β, IL-6 and IL-12 are central regulators of the inflammatory process orchestrated by Th1 cells. These cytokines boost the expression of other cytokines and chemokines, adhesion molecules, matrix metalloproteinases, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2). PARP inhibition or the PARP-1 knockout genotype has been shown to result in suppressed levels of the inflammatory cytokines in various animal models of inflammation. Similarly, many chemoattractant chemokines (e.g. IL-8, MIP-1, MIP-2, MCP-1) were also found to be downregulated in animals lacking a functional PARP-1 gene or treated with a PARP inhibitor. These changes may represent the underlying mechanism for the inhibition of inflammatory cell migration as reported in many Th1-mediated inflammatory conditions.

PARPs other than PARP1 may also alter the production of chemokines and cytokines. Deletion of PARP-2 leads to alterations in the transcriptome, notably in the expression of genes involved in inflammatory regulation [reviewed in [35]]. Interestingly there seems to be an overlap with the inflammatory genes dysregulated upon PARP-1 ablation: e.g. Il-1β and TNFα levels were lowered both in the absence of PARP-1 or PARP-2 [36,37]. Moreover, knocking out PARP-14 enhances IL-4-induced STAT6-mediated gene expression that impacts on immune processes notably in Th2-mediated processes in the lungs [30,31].

3.3. Adhesion factors

Another important group of regulated proteins include different adhesion proteins, such as cell adhesion molecules (I-CAM, V-CAM, L-CAM) and selectins. Suppressed expression of adhesion molecules on the surface of endothelial and immune cells decreases the migration of inflammatory cells to the site of inflammation and thus inhibits inflammation. In the absence, or upon inhibition of PARP-1, the expression of these adhesion molecules is depressed [21,38]. This effect may have a dual cause: on one hand NFκB directly regulates the expression of these genes, while on the other hand, a secondary loop may exist, where the NFκB-regulated cytokines regulate the expression of the adhesion molecules [39,40].

3.4. Inflammatory mediators: iNOS, COX-2 and MMPs

An important inflammatory gene regulated by PARP-1 is iNOS that is responsible for NO synthesis under inflammatory conditions [41,42]. NO derived from iNOS may combine with superoxide to form peroxynitrite [43–45]. Interestingly, iNOS, under certain pathological conditions, where iNOS substrates are limiting, may become uncoupled and produce superoxide instead of nitrogen monoxide [46]. This mechanism has been suggested to enhance peroxynitrite production and tissue damage [47]. Although it is a rather labile reactive nitrogen species, peroxynitrite can travel through biological compartments, can diffuse through membranes and can reach the nucleus to trigger oxidative and nitrative damage to DNA, proteins and lipids [48].

As iNOS is regulated via NFκB activation, therefore PARP inhibition is capable of markedly reducing iNOS expression and nitrosative stress [21,39]. Cyclooxygenase-2 (COX-2) is also involved in generating free radicals and has been shown to be regulated by NFκB. In the case of COX-2, however, a more direct regulatory link may be more important: PARP-1 has been demonstrated to bind to the mouse COX-2 promoter region through interactions with the inhibitory element resulting in the inhibition of COX-2 expression [49].

Increased oxidative stress is capable of inducing redox-sensitive enzymes, such as matrix metalloproteinases (MMPs). In addition to proteolytic cleavage, MMPs can also be activated by free radical-induced structural changes [50] and are indispensable for cellular movements within tissues. Several studies have shown that MMP activation during inflammation (e.g. MMP-9 activation in skin inflammation) can be prevented by knocking out PARP-1 or by

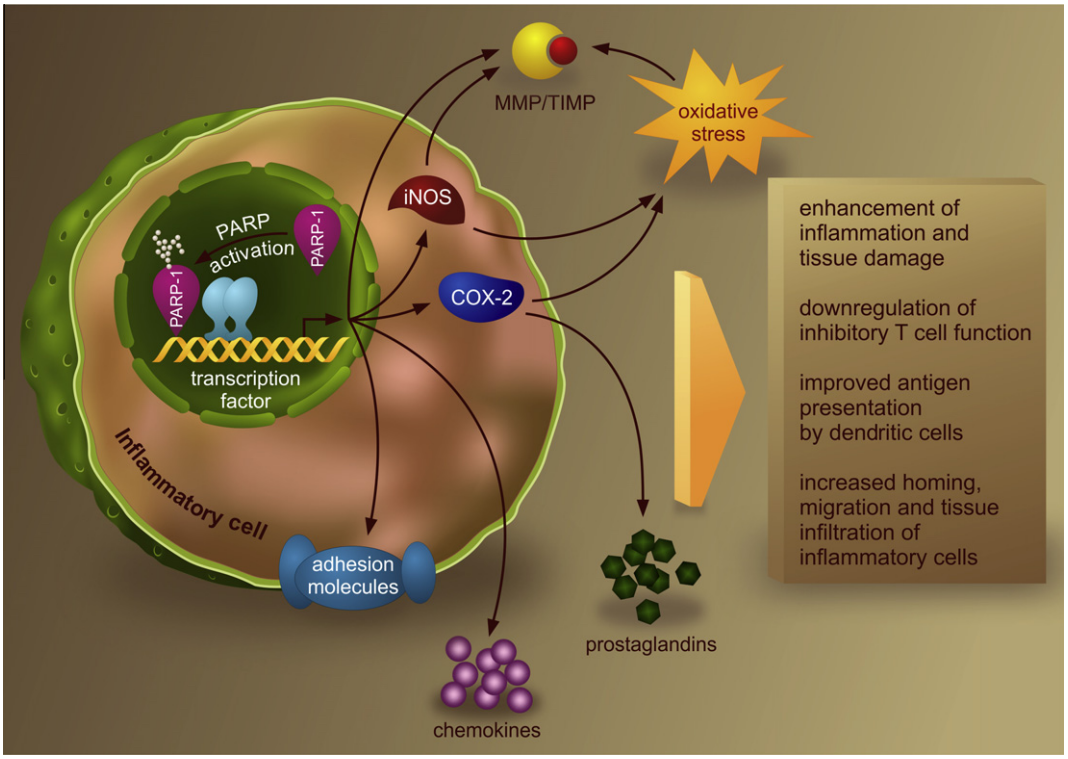

Fig. 1. PARP as a central regulator of inflammatory pathways. DNA damage triggers the activation of PARP-1 and -2. PARP activation has proinflammatory properties through lowering the number of inhibitory T cells, enhancing antigen presentation by dendritic cells. Moreover, oxidative stress stimulates redox-sensitive transcription factors that are co-activated by PARP-1. These transcription factors regulate the expression of chemokines, adhesion molecules, iNOS, MMP and COX-2. These effects lead to inflammatory cell homing, tissue invasion and activation which in turn further enhances inflammation-related oxidative stress and a vicious, self-intensifying cycle of inflammation.

pharmacological PARP inhibition [21,51–54]. Moreover, tissue inhibitors of MMPs (TIMPs) that keep MMP activity under control are inversely regulated with MMPs [21,51,54]. It has not been determined as of yet whether these effects are related to modulation of MMP and TIMP gene expression by PARylation or PARylation controls MMP activation via regulation of cellular redox status.

From the above it is clear that PARP-1 plays a central role in inflammation by influencing multiple key events such as the production of cytokines, expression of adhesion molecules, iNOS and COX-2 and probably MMPs and TIMPs through modulating different transcription factors (Fig. 1.). These events form a complex signaling network in which the proteins display a multilevel interrelationship with each other. For example NFκB enhances iNOS expression, hence oxidative stress that in turn activates both NFκB and PARP-1/2, creating a vicious, self intensifying cycle. Moreover, the PARP-1/2- and NFκB-dependent expression of adhesion factors and MMPs contribute to inflammatory cell migration and thus to oxidative stress which feeds back to both PARP-1/-2 and NFκB. This high level of complexity makes the in vivo dissection of causal relationships challenging. In the same time this central role of PARP-1 in inflammatory circuitry makes these enzymes promising targets of anti-inflammatory drug development.

4. Oxidative stress-induced activation of poly(ADP-ribose) polymerases in inflammation

Inflammatory processes are associated with high level of oxidative stress. The oxidants produced for example by iNOS, NADPH oxidases, COX-2 or the mitochondrial respiratory chain cause excessive DNA damage. Berger and colleagues [55] proposed that severe DNA damage may lead to excessive PARP activation which may deplete cellular NAD^+ pools compromising cellular metabolism. Under such conditions glycolytic flux slows down [56] thereby impairing an oxygen-insensitive metabolic pathway. Moreover, NAD^+ depletion turns on NAD^+ resynthesis via nicotinamide mononucleotide adenylyltransferase (NMNAT) and phosphoribosyl pyrophosphate synthetase (PPS) at the expense of ATP. The often marked NAD^+ depletion may lead to consumption of cellular ATP [3,55]. Under low ATP, low NAD^+ conditions, mitochondrial F1/F0 ATPase turns to function as ATPase rather than ATP synthase [57] further deteriorating energy depletion. Compromised cellular energetics may contribute to the pathological sequalae of excessive poly(ADP-ribosyl)ation in inflammations.

In severe oxidative stress, cellular energy status also affects cell death pathways. Failure of DNA repair initiates apoptotic cell death. Since apoptosis also relies on ATP, cleavage of PARP-1 and -2 by caspase-3 and -7 may be viewed as a preventive measure aiming at the conservation of cellular ATP [58,59]. During apoptosis cellular content is crosslinked and cells disintegrate into membrane-coated vesicles marked with the "eat-me" signal phosphatidyl-serine for phagocytosis. These vesicles are then cleared by infiltrating macrophages and resident, neighboring cells, therefore no leakage of cellular content occurs under apoptosis.

If the apoptotic process cannot be executed (e.g. due to lack of sufficient amount of ATP or inhibition of caspases), then cells may die by necrosis. Necrosis is characterized by the lack of the morphological and biochemical hallmarks of apoptosis. Most notably, plasma membrane integrity is compromised early during necrosis and cellular content may leak into the environment. Such leakage may cause secondary tissue injury by causing further inflammation. Initially necrosis was thought to be an uncontrolled form of cell death. However, recently programmed features and necrotic signaling molecules (RIP kinases, non-caspase proteases, cyclophylline D) have been identified in necrosis indicating that necrosis is not necessarily beyond regulatory control [60]. Overactivation of PARP-1 has been increasingly recognized as a mediator of necrosis that is highly amenable to pharmacological intervention. In severe oxidative stress for example PARP-1-mediated necrosis serves as a

backup mechanism eliminating severely injured cells even when the apoptotic machinery is incapacitated. In fact PARP activation actively switches the default apoptotic cell death towards necrosis. When PARP activity is inhibited or parp-1 gene is knocked out, necrosis can be reverted to apoptosis [3,61–63].

5. Inflammatory diseases mediated by poly(adp-ribose) polymerases

Previously we reviewed the molecular determinants for the proinflammatory role of PARylation. These mechanisms have been validated in a vast array of inflammatory conditions identifying a large number of diseases where PARP inhibition may provide therapeutical benefits (detailed in Table 1.). It is important to note that almost all organs display inflammatory conditions that can be attenuated by PARP inhibition indicating that PARP affects central events in inflammatory signaling. The diseases listed in Table 1 are quite diverse in terms of etiology, pathomechanism (infectious, autoimmune, allergic, irritation-induced, etc.) being organ-restricted versus generalized inflammations. Most of the conditions listed are mediated by IL-2- and IFNγ-producing Th1 cells. Others such as asthma are typical Th2-mediated conditions dominated by the production of Th2 cytokines such as IL-4, -5 and -14. Recent reinterpretation of Th1/Th2 dichotomy as triggered by the identification of the novel Th17 cell type shed light on the complexity of immunoregulation in inflammatory diseases such as collagen-induced arthritis (CIA) and experimental allergic encephalomyelitis (EAE), animal models of the human diseases rheumatoid arthritis and multiple sclerosis, respectively. These latter two models are now considered as Th17 rather than Th1-mediated conditions. (The new Th17 cell type is characterized by the production of IL17 and 23.)

Since PARP-1 regulates such central events of inflammatory signaling as the activation of NFκB and AP-1 transcription factors, therefore it is not surprising that PARP inhibition has beneficial effects in a wide spectrum of inflammatory conditions. Nonetheless, the mechanism of the beneficial effects of PARP inhibition may differ between Th1 and Th2-mediated conditions. Whereas the NFκB co-activator function of PARP-1 has been made responsible for the effects of PARP inhibitors in Th1 diseases (and this may also contribute to the pathology of Th2-mediated conditions), recently a novel mechanism has been described for asthma, a prototypical Th2-mediated disease. Datta et al. [64] have demonstrated in a murine model of asthma that inhibition of eosinophil migration in PARP-$1^{-/-}$ mice is controlled at a step downstream of IL-4 and upstream of IL-5. PARP-1 was found to stabilize STAT-6 protein (without affecting mRNA) in an allergen-stimulation dependent manner. STAT-6, a central regulator of IL-5 expression undergoes degradation in the absence of functional PARP-1. This example nicely illustrates that the role played by PARPs in inflammation is complex and may differ in various forms of inflammation.

An inflammatory component has recently been identified as an important pathogenetic factor in the development of several chronic diseases of the cardiovascular system such as atherosclerosis, chronic heart failure and cardiovascular aging [65]. Both PARP inhibition and knockout of PARP-1 have been shown to have beneficial effects in murine models of these conditions [66–70]. Although the molecular mechanisms underlying these positive effects are not well understood, it is plausible to hypothesize that the anti-inflammatory effects of PARP inhibition may contribute to improved clinical parameters observed in these models. PARP activation is associated with numerous human inflammatory diseases such as allograft rejection, various forms of shock, arthritis, colitis, diabetic complications, transplant rejection, COPD [3,71,72] opening the door for the possible clinical use of PARP inhibitors in these diseases. Several clinical trials have been conducted with PARP inhibitors demonstrating their good tolerability [73,74] and their potential as anti-cancer agents [75]. Moreover, in the study

Table 1
Inflammatory diseases mediated by poly(ADP-ribosyl)ation. PARPi – PARP inhibition, KO – knockout, all other abbreviations in text.

Organ	Disease	Protection provided by	Ref.
Multiorgan diseases	Sepsis	PARPi	[82]
	Endotoxic shock	PARP-1 K.O., PARPi	[16,83]
	Heamorrhagic shock	PARP-1 K.O.	[84]
Central nervous system	Allergic encephalomyelitis	PARPi	[85]
	Meningitis-related central nervous system complications	PARP-1 K.O., PARPi	[86]
	Myelitis	PARPi	[87]
	Astrocyte activation	PARP-1 KO	[36]
		PARP-2 KO	
		PARP-3 KO	
Joints	Arthritis		[88]
	Temporomandibular joint disorder	PARPi	[89]
Bones	Cherubism	Tankyrase activation	[79]
GI tract	Colitis	PARP-1 and -2 K.O.	[37,38]
	Pancreatitis	PARP-1 K.O. (PARP-2 has no effect), PARPi	[90]
	Peritonitis	PARP-1 K.O.	[91]
Respiratory system	Asthma	PARPi	[64,92–94]
		PARP-14 activation	[31]
	COPD	–	[95]
	Pleuritis	PARPi	[96]
	ARDS	PARP-1 K.O., PARPi	[97]
	Ventilation-induced inflammation	PARPi	[98]
	Rejection of tracheal allografts	PARPi	[99]
Skin	Contact hypersensitivity	PARP-1 K.O., PARPi	[21,51,100]
	Irritative dermatitis	PARP-1 K.O., PARPi	[21,51]
	Sunburn-related dermal inflammation	PARPi	[101]
Eye	Uveitis	PARPi	[102]
Ear	Cochlear lateral wall damage	PARP-1 K.O.	[103]
Skeletal muscle	Movement-induced damage associated inflammation		[104]
Kidneys	Renal hypertrophy	PARPi	[105]
	Cisplatin-induced kidney inflammation	PARPi, PARP-1 K.O.	[106]
	Diabetic nephropathy	PARPi	[107,108]
Cardiovascular system	Atherosclerosis	PARPi	[54,109–111]

utilizing the PARP inhibitor INO1001, Morrow and colleagues have shown that administration of INO1001 resulted in a tendency to reduce IL-6 and CRP levels pointing towards suppressed inflammation [73].

In addition to the beneficial effects of PARP inhibitors and protection provided by knockout phenotypes, the role of PARPs in inflammation is also indicated by association of certain PARP-1 promoter haplotypes and SNPs with diseases. Such associations have been reported for systemic lupus erythematosus [76], autoimmune nephritis [76] or rheumathois arthritis [77] further supporting a possible link between PARP-1 and autoimmune inflammation.

6. Conclusion

As detailed above, PARP activation is a key event in the propagation of inflammation and PARP inhibition suppresses inflammation at multiple molecular events (for overview, see Fig. 1). Key components of the anti-inflammatory effects of PARP inhibition are the following: (1) Members of the PARP family may be necessary for the maturation and differentiation of cells of the immune system with PARP-1 and -2 playing a role in the regulation of T cell function. (2) PARPs are integral and central players of the self intensifying circle of inflammation by regulating the expression of inflammatory mediators such as cytokines, chemokines, adhesion molecules, iNOS and COX-2. A key molecular event in this regulation is the interaction of PARP-1 with transcription factors such as NFκB and AP-1. (3) Free radicals may cause DNA damage and activate PARP-1 and -2. In case of severe DNA damage, PARP overactivation may cause cell dysfunction and cell death which may contribute to inflammation accompanying severe conditions such as shock and ischemia–reperfusion injuries.

Several open questions concerning PARP-related inflammatory diseases remain to be resolved. These include but are not limited to the mechanism of gender bias described in the role of PARP in inflammations [78]. Furthermore, it will be important to determine the involvement of further members of the PARP family in the regulation of inflammatory processes. Some of them have already been shown to associate with inflammatory pathologies: such as PARP-2 (reviewed in [35]), PARP-3 [36], tankyrases [79], or PARP-14 [30,31]. Moreover, poly(ADP-ribose) glycohydrolase has been implicated in the regulation of immune functions [80,81] underlining the central role of poly(ADP-ribosyl)ation in inflammation. A key question is whether the powerful anti-inflammatory effects of PARP inhibitors as observed in animal models can be translated to human diseases and to determine the risk benefit ratio of acute and chronic administration of PARP inhibitors in non-cancer patients.

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